

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 15

#### **REMARKS**

Claims 1, 21, 27, 28, 33-38, 42, 44-49, 53, 55-59, 61, 80, 81, 83-86, 90, 91 and 94 are pending in the subject application. The Examiner has withdrawn claims 1, 21, 33-36, 42, 44-49, 53, 55-59, 61, 80, 81, 83-86, 90, 91 and 94 from further consideration. Applicants have hereinabove cancelled claims 1, 21, 27, 28, 33-36, 42, 44-49, 53, 55-59, 61, 80, 81, 83-86, 90, 91 and 94 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed continuing application. Applicants have also amended claims 37 and 38 and added new claims 97-101. Support for these amendments may be found, inter alia, in the specification as follows: claims 37, 38, 99 and 100: page 82, lines 34-35; page 88, lines 30-32; page 91, lines 4-6; Table 2 on page 101; and Table 5, description of crystal type E; claims 97 and 98: page 134, lines 15-27; claims 101-106: page 40, lines 1-3. Applicants maintain that these amendments raise no issue of new matter. Accordingly, upon entry of this amendment claims 37, 38 and 97-106 will be pending and under examination.

#### **Sequence Compliance**

The Examiner stated that the instant application contains at least one nucleic acid and/or amino acid sequence that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). The Examiner stated that as such, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825. a) The Examiner stated that the structural coordinates in Figures 53-1 to 53-111, i.e., atoms 1 to 2300, atoms 2496

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 16

to 3907, atoms 3909 to 5553 and atoms 5555 to 7277, teach several amino acid sequences since a particular amino acid is assigned to a linear sequence in a particular order. The Examiner stated that as such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID NO must be inserted into the brief description of the drawings or into the Figure directly. The Examiner stated that the sequence alignment in Figures 29D-1 and 29D-2 teaches several amino acid sequences.

The Examiner stated that applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. The Examiner stated that if the noted sequences are not in a sequence listing, applicants must provide (1) a copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

In response, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application enclose a computer diskette containing the sequence listing in computer readable form. Applicants attach hereto, as **Exhibit A**, a paper copy of the computer readable form of the sequence listing. Applicants attach hereto as **Exhibit C** a Statement in Compliance with 37 C.F.R. §1.821(f) certifying that the computer readable form contains the same

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 17

information as the paper copy of the sequence listing attached as **Exhibit A**.

In addition, applicants have hereinabove amended the specification to include references to the sequence identifier information (i.e., SEQ ID NO:) as required by 37 C.F.R. §1.821(d). This amendment does not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested.

#### Specification/Informalities

The Examiner stated that the title of the invention is not descriptive. The Examiner required a new title that is clearly indicative of the invention to which the claims are directed.

In response, applicant has herein amended the Title of the Invention as suggested by the Examiner. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of objection.

The Examiner objected to the Abstract for allegedly not completely describing the disclosed subject matter. The Examiner suggested including the full name of the source species (i.e. human CD4 and HIV type), for completeness.

In response applicant respectfully traverses. Nevertheless, without conceding the correctness of the Examiner's objection and to expedite prosecution of the subject application, applicants have herein amended the abstract such that it now recites "human CD4" and HIV "Type 1" where appropriate as

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 18

recommended by the Examiner. Applicants maintain that these amendments do not involve any issue of new matter. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of objection.

**Claim Rejections Under 35 U.S.C. §112, Second Paragraph**

The Examiner rejected claims 27, 28, 37 and 38 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to the Examiner's rejection of claims 27 and 28, but without conceding the correctness thereof, applicants note that these claims have been cancelled without prejudice or disclaimer. Thus, the rejection thereof is moot.

The Examiner alleged that the claims are indefinite because of the use of the term "portion" or "portion of gp120". The Examiner asserted that neither the specification nor the claims provides a clear definition of what is intended by the term "gp120" or a "portion" thereof: what characteristics distinguish a "gp120" glycoprotein from any other glycoprotein such that a skilled artisan could identify the intended scope of "gp 120." The Examiner further asserted that because the specification fails to define a "portion" or what is intended as being encompassed by the term, it is unclear as to that part of a "gp120" that is considered to be a "portion" and that part that is not: is the term "portion" meant to be interpreted as a single atom? A single amino acid? Ten contiguous amino acids of the primary sequence? A particular,

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 19

localized tertiary structure or fold? The Examiner required clarification of the metes and bound of the claims.

In response to the Examiner's rejection of claims 37 and 38, applicants respectfully traverse, noting that claims 37 and 38, as amended, address the issues set forth above by the Examiner. Specifically, these claims have been amended such that they no longer recite the term "portion." Applicants maintain that these amendments do not involve any issue of new matter. Accordingly, applicants contend that claims 37 and 38, as amended, satisfy the requirements of 35 U.S.C. §112, second paragraph, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner further asserted that the claims are indefinite because it is unclear as to how a skilled artisan is to determine a binding site, determine whether a compound would fit, and/or design a compound as encompassed by the claims: Are these meant to be purely mental steps, active method steps, or a combination thereof. The Examiner stated that if they are meant as active method steps, what process or processes are involved in such "determining" or "designing" steps?

In response to the Examiner's rejection of claims 37 and 38, applicants respectfully traverse, noting that claims 37 and 38, as amended, address the issues set forth above by the Examiner. Applicants note that methods for identifying and designing compounds based on X-ray crystallography data are set forth on pages 31-34 of the subject specification. Accordingly, applicants contend that claims 37 and 38, as

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 20

amended, satisfy the requirements of 35 U.S.C. §112, second paragraph, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**Claim Rejections Under 35 U.S.C. §112, first paragraph**

Written Description

The Examiner rejected claims 27, 28, 37 and 38 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner stated that the instant claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner asserted that the claims encompass subject matter that is not defined nor appropriately described in the specification. The Examiner stated that claims 27 and 28 are directed to a method for identifying or designing a gpl20 associating compound relying on the use of all possible atomic coordinates that can be determined from all possible crystals of a "portion of gpl20." The Examiner stated that claims 37 and 38 are directed to a computational based method for identifying or designing compound capable to the CD4 binding site relying on the use of a "portion" from all possible atomic coordinates that can be determined from all possible crystals of a "portion of gpl20" capable of binding to CD4. The Examiner stated that the specification lacks adequate written description to demonstrate to a skilled artisan that applicant was in possession of the claimed invention.

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 21

The Examiner stated that the specification has given no concise definition of the "portion" and said term does not impart any structural limitations on the gpl20, crystals and derived atomic coordinates thereof. The Examiner stated that the specification neither describes nor exemplifies all possible portion of the protein that demonstrates a biological activity and structure characteristic of the protein. The Examiner stated that there are no requirements as to whether the atomic coordinates of instant method have atoms that are covalently attached or separated by a distance within the radius of gyration of the polypeptide, only that the atomic coordinates represent a "portion" of gpl20. The Examiner stated that the polypeptide "gpl20" as recited in the claims lacks a clear and concise structural and functional correlation for the claimed genera of polypeptides.

The Examiner stated that although applicants seem to establish that the "gpl20" polypeptides encompassed by the broad claims is a reengineered full-length polypeptide from an HIV source for crystallization purposes, there is allegedly no clear description (e.g., by sequence identifier, number of amino acid residues or nucleotides, etc).

The Examiner stated that in this case, the specification discloses only a single representative species of structural coordinates comprising a "portion" of gpl20, i.e., Figures 52-1 to 51-122, obtained from a single representative of a crystalline form comprising a "portion" of gpl20, i.e., trimeric complex between fully deglycosylated HIV-1 gpl20 construct  $\Delta 82\Delta V1/2*\Delta V3\Delta C5$ , D1D2 sCD4 and Fab 17b (citing Table

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 22

2, 4, 5 and 6 at pp. 103-106). The Examiner stated that this single representative crystalline form fails to reflect the variation of polypeptide species, crystalline forms and structural coordinates thereof as encompassed by the claims. The Examiner stated that other than this single representative species, the specification fails to describe any additional species by any relevant, identifying characteristics or properties. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The Examiner stated that the claimed genera of gp120 polypeptides, crystalline forms and derived atomic coordinates thereof are widely variant and not defined by a specific correlation between structure and/or function of the polypeptides, crystalline forms thereof and corresponding atomic coordinates representing the widely variant polypeptide forms.

The Examiner concluded that given the lack of description of a representative number of polypeptides, crystalline forms and atomic coordinates thereof, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention. The Examiner stated that at best, it simply indicates that one should run tests on a wide spectrum of portions of gp120 in the hope that at least one of them can be isolated, crystallize and lead to a suitable screening three-dimensional model.

In response to the Examiner's rejection of claims 27 and 28, but without conceding the correctness thereof, applicants note

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 23

that these claims have been cancelled without prejudice or disclaimer. Thus, the rejection thereof is moot.

In response to the Examiner's rejection of claims 37 and 38, applicants respectfully traverse, noting that claims 37 and 38, as amended, address the issues set forth above by the Examiner. Specifically, these claims have been amended such that they no longer recite the term "portion," but instead are directed to the specific trimeric complex between deglycosylated HIV-1 gp120, D1D2 CD4 and Fab 17b which the Examiner conceded is adequately described in the subject specification. Applicants maintain that these amendments do not involve any issue of new matter. Accordingly, applicants contend that claims 37 and 38, as amended, satisfy the written description requirement of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

#### Enablement

The Examiner rejected claims 27, 28, 37 and 38 under 35 U.S.C. §112, first paragraph for alleged lack of enablement.

The Examiner conceded that the specification is enabling for *in silico* screening of compounds using the full-set of atomic coordinates or a defined binding pocket within said full-set, as set forth in Figures 52-1 to 51-122, obtained from the X-ray diffraction data of a crystal consisting of the trimeric complex between fully deglycosylated HIV-1 gp120 construct Δ82ΔV1/2\*ΔV3ΔC5, D1D2 sCD4 and Fab 17b (citing Table 2, 4, 5 and 6 at pp.103-106).

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 24

However, the Examiner asserted that the specification does not reasonably provide enablement for making new crystals consisting of a "portion" of gpl20 from which a three-dimensional model can be generated.

The Examiner asserted that in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior and current state of the art, and the amount of experimentation required to make all structural coordinates obtained from crystallographic data as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. The Examiner also asserted that applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The Examiner further asserted that without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

In response to the Examiner's rejection of claims 27 and 28, but without conceding the correctness thereof, applicants note that these claims have been cancelled without prejudice or disclaimer. Thus, the rejection thereof is moot.

In response to the Examiner's rejection of claims 37 and 38, applicants respectfully traverse, noting that claims 37 and 38, as amended, address the issues set forth above by the

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 25

Examiner. Specifically, these claims have been amended such that they no longer recite the term "portion," but instead are directed to the specific trimeric complex between deglycosylated HIV-1 gp120, D1D2 CD4 and Fab 17b which the Examiner conceded is enabled by the subject specification. Applicants maintain that these amendments do not involve any issue of new matter. Accordingly, applicants contend that claims 37 and 38, as amended, satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**Claim Rejection Under 35 U.S.C. §103(a)**

The Examiner rejected claims 27, 28, 37 and 38 under 35 U.S.C. §103(a) as allegedly unpatentable over Balaji et al. (U.S. Patent 5,579,250, "Balaji") in view *In re Gulack* (217 USPQ 401 (Fed. Cir. 1983)) and *In re Ngai* (70 USPQ2d 1862 (Fed. Cir. 2004)).

The Examiner asserted that the claims are drawn to a computational based method for identifying or designing a compound capable of binding a "portion" of gp120 or to the CD4 binding site of gp120 using atomic structure coordinates of a portion of gp120.

The Examiner stated that Balaji teaches methods of rational drug design via computer modeling. The Examiner stated that columns 11-32 detail the use of atomic coordinates of a receptor - such as a protein - wherein drugs or compounds which interact therewith are designed using structural

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 26

coordinate data obtained from, e.g., X-ray crystallography. The Examiner stated that polypeptide modeling is specifically discussed in column 24, line 50, through column 25, line 26. The Examiner stated that in columns 11-32, energy minimization, bond angles, etc. are discussed as parameters in said design methods, including those of making and contacting compound with protein. The Examiner stated that these descriptions are encompassed by the instant methods, only missing the specific structural coordinates as disclosed in Figures 52-1 to 51-122.

The Examiner stated that in *Gulack and Ngai*, the court held that nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability. The Examiner stated that the key factor in analyzing the obviousness of these claims over the prior art is the determination that the computer algorithm used to identify compounds that may bind gpl20 is a known algorithm and is unmodified. The Examiner stated that if the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. The Examiner stated that in this case, the structural coordinates disclosed in Figures 52-1 to 51-122 are nonfunctional descriptive material and the method uses a known unmodified computer algorithm. The Examiner stated that data, which are fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps, do not impose a change in the processing steps and are thus nonfunctional descriptive material. The Examiner stated

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 27

that a method of using a known comparator for its known purpose to compare data sets does not become non-obvious merely because new data becomes available for analysis. The Examiner stated that nonfunctional descriptive material cannot render non-obvious an invention that would have otherwise been obvious (citing MPEP 2106 and Cases 6-7 of the "Report on comparative study on protein three-dimensional structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" at [www.uspto.gov/web/tws/wm4/wm4-index.htm](http://www.uspto.gov/web/tws/wm4/wm4-index.htm)).

The Examiner stated that as nonfunctional data used in a known algorithm do not modify any of the processing steps, and simply changing the data to be processed is not beyond the ordinary skill in the art, it would have been obvious at the time of the invention to perform rational drug design as taught by Balaji to result in a compound that interacts with gpl20 or a portion of gpl20, wherein only nonfunctional descriptive material is additionally present in the claims, which do not distinguish the claimed methods from Balaji according to *In re Gulack* and *In re Ngai*.

In response to the Examiner's rejection of claims 27 and 28, but without conceding the correctness thereof, applicants note that these claims have been cancelled without prejudice or disclaimer. Thus, the rejection thereof is moot.

In response to the Examiner's rejection of claims 37 and 38, applicants respectfully traverse, and maintain that the Examiner has failed to establish a prima facie case of obviousness against the rejected claims.

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 28

The Examiner has cited MPEP §2106 which is entitled "Patentable Subject Matter" in support of his rejection. However, applicants note that MPEP §2116.01 applies to obviousness rejections under 35 U.S.C. §103(a), not MPEP §2106. Pursuant to MPEP §2116.01:

"All the limitations of a claim must be considered when weighing the differences between the claimed invention and the prior art in determining the obviousness of a process or method claim. See MPEP 2143.03.

*In re Ochiai*, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 77 F.3d 422, 37 USPQ2d 1663 (Fed. Cir. 1996) addressed the issue of whether an otherwise conventional process could be patented if it were limited to making or using a nonobvious product.

To support a rejection under 35 U.S.C. 103, the collective teachings of the prior art must have suggested to one of ordinary skill in the art that, at the time the invention was made, applicant's claimed invention would have been obvious. In applying this test to the claims on appeal in *Ochiai* and *Brouwer*, the court held that there simply was no suggestion or motivation in the prior art to make or use novel, nonobvious products in the claimed processes. Consequently, the court overturned the rejections based upon 35 U.S.C. 103.

Interpreting the claimed invention as a whole requires consideration of all claim limitations. Thus, proper claim construction requires treating language in a process claim

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 29

which recites the making or using of a nonobvious product as a material limitation. Motivation to make or use the nonobvious product must be present in the prior art for a 35 U.S.C. 103 rejection to be sustained. The decision in *Ochiai* specifically dispelled any distinction between the processes of making a product and methods of using a product with regard to the effect of any product limitations in either type of claim."

Briefly, applicants note that claims 37 and 38, as amended, are directed to methods of using atomic coordinates of a novel trimeric complex comprising specific portions of deglycosylated HIV-1 gp120, D1D2 CD4 and Fab 17b to identify or design compounds capable of binding to the CD4 binding site of HIV-1 glycoprotein gp120. Such methods include, but are not limited to, model building techniques and computer evaluation systems as described on pages 31-34 of the subject specification.

Balaji et al. teach methods of rational drug design using computer modeling. However, this patent does not teach the use of atomic coordinates of applicants' novel trimeric complex recited in amended claims 37 and 38.

At issue in *In re Gulack* are claims which are directed to a device comprising a band and the digits printed thereon. However, nowhere does the court in *Gulack* discuss the obviousness of any method which uses a novel composition. Therefore, *In re Gulack* is not pertinent to an analysis of applicants' claimed methods.

At issue in *In re Ngai* are claims directed to a kit containing

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 30

instructions describing a *new method* for using a *known product* and the known product. However, nowhere does the court in *Ngai* discuss the obviousness of any method which uses a *novel product or composition*. Therefore, *In re Ngai* is not pertinent to an analysis of applicants' claimed methods.

In addition, with respect to the "Report on comparative study on protein three-dimensional structure related claims" of the "Trilateral Project WM4 Comparative studies in new technologies" cited by the Examiner, applicants note that this report is neither a law, a rule or any guideline promulgated by the United States Patent and Trademark Office and therefore cannot serve as a basis for an obviousness rejection.

According to MPEP §2116.01, to support a case of prima facie obviousness, *Balaji et al.*, *In re Gulack* and *In re Ngai*, when combined, would have to teach or suggest all elements of the rejected claims. Again, one element of each of applicants' rejected claims is a novel trimeric complex comprising specific portions of deglycosylated HIV-1 gp120, D1D2 CD4 and Fab 17b. Thus, at the very least, these references would have to teach or suggest this novel trimeric complex.

*Balaji et al.*, in view of *In re Gulack* and *In re Ngai*, does not teach or suggest the trimeric complex comprising specific portions of deglycosylated HIV-1 gp120, D1D2 CD4 and Fab 17b recited in amended claims 37 and 38, and thus does not teach or suggest all elements of the rejected claims.

Accordingly, the Examiner has failed to establish the prima facie obviousness of claims 37 and 38 over these references.

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 31

In view of the above remarks, applicants maintain that claims 37 and 38 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**Summary**

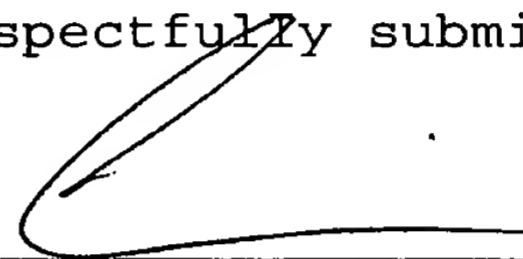
In view of the remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

Applicants : Peter D. Kwong et al  
Serial No. : 09/856,200  
Filed : January 3, 2003  
Page 32


No fee, other than the enclosed fee of \$510.00 fee for a three-month extension of time, is deemed necessary in connection with this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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11/15/06  
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# Exhibit B